standard DNA at the selected excessiveness of said sample DNA, wherein said exchange occurs at a higher frequency when the target DNA is the same as the labeled standard DNA, and said label intensity is reduced.--

REMARKS

Claims 1-10 are pending in the present application. Claims 11 and 12 are newly added for consideration by the Examiner. These claims are added to better and more fully described the present invention. Support for the newly added claims 11 and 12 is found in the specification, especially page 19, lines 14-20, and in the original claims 1 and 2, and 2 and 3, respectively. Claims 2 and 3 have been amended to better place the claims into condition for allowance. No new matter is inserted into the application.

Request for Initialed PTO-1449

Applicants hereby respectfully request the Examiner provide an initialed copy of the PTO-1449 form, which was originally submitted with an Informational Disclosure Statement on January 11, 1999. Applicants have resubmitted a copy of the PTO-1449 form for the Examiner's convenience.

Issues under 35 U.S.C. § 112, second paragraph

Claim 2

The Examiner has rejected claim 2 under 35 U.S.C. § 112, second paragraph, for being indefinite. The rejection applied to this pending claim is respectfully traversed. Reconsideration and withdrawal thereof is requested.

The Examiner argues in the outstanding Office Action that it is unclear what "A/B" and "B/A" mean in claim 2. In response to the Examiner's remarks, Applicants amend claim 2 to recite that A/B is the fractional equivalent of the percentage of target DNA content in the sample DNA. As such, Applicants submit that the amended claim fully clarifies the meaning of the "A/B", and thusly any rejection applied to this claim is rendered moot.

Claim 3

The Examiner has rejected claim 3 under 35 U.S.C. § 112, second paragraph, for being indefinite. The rejection applied to this pending claim is respectfully traversed. Reconsideration and withdrawal thereof is requested.

In the outstanding Office Action, the Examiner argues that the term "utilizing theoretical values" renders claim 3 indefinite. In response to the Examiner's remarks, Applicants have removed this language from claim 3. Applicants further add

to the claim that said exchange occurs at a higher frequency when the target DNA is the same as the labeled standard DNA, and said label intensity is reduced. As such, Applicants submit that the amendment to the instant claim 3 renders it definite, and thusly any rejection applied to this claim is rendered moot.

Claims 1-3 and 7-9

The Examiner has rejected claims 1-3 and 7-9 under 35 U.S.C. § 112, second paragraph, for being indefinite. The rejection applied to these pending claims is respectfully traversed. Reconsideration and withdrawal thereof is requested.

The Examiner argues that the term "labeled standard DNA" as recited in the above-mentioned claims is indefinite. Applicants submit that page 16, line 18-22 of the instant specification clearly defines what is the "labeled standard DNA". Furthermore, the "labeled standard DNA" terminology is well known in the art. Even other publications referenced by the Examiner, i.e. Nicolas et al. and Carson '251, use the "standard DNA" term. See the abstract, line 4-5, of Nicolas et al., and column 12, lines 17-21 of Carson '251. Therefore, one skilled in the art will know what is meant by the term "labeled standard DNA."

Issues Under 35 U.S.C. § 103

The Examiner has rejected claims 1, and 4-10 under 35 U.S.C. § 103 as obvious over Li '356 (US 5,500,356), de la Chapelle '808 (US 5,492,808), and Carson '251 (US 5,747,251). Specifically, the Examiner argues that it would be obvious to one skilled in the art to combine the teachings of the three references to produce the present invention. The rejection applied to these pending claims is respectfully traversed. Reconsideration and withdrawal thereof is requested.

Li '356

Li '356 discloses a method to rapidly isolate and recover target DNA and RNA molecules from a mixture or a library. The isolation of the target molecules is accomplished by hybridizing the desired target molecules with complementary haptenylated probes. The resulting hybrids are subsequently passed through an affinity column, thereby capturing the target molecules. The single-stranded target molecules are released and amplified with a nucleotide analog that confers endonuclease resistance. Subsequent restriction digests will degrade those molecules without the endonuclease resistance. Li '359 fails to disclose using this invention as a method to search for DNA mutations.

de la Chapelle '808

De la Chapelle '808 discloses a diagnostic kit for detection of familial colon cancer. De la Chapelle '808 discloses a polymorphism on chromosome 2p13-21 that linked to familial colon cancer. This polymorphism may be detected by any method well known in the art, such as Southern blotting, PCR amplification, etc. De la Chapelle '808 fails to disclose a method for determining any mutant gene other than the mutation found on chromosome 2.

Carson '251

Carson '251 discloses a method to detect and quantify target nucleic acids in a sample by combining ELISA and PCR protocols. In this method a known amount competitor nucleic acid molecule is co-amplified along with the target molecule. The competitor nucleic acid is designed with one or more nucleotide changes from the target nucleic acid. The primer is then used in PCR reactions to incorporate a coupling agent to the nucleic acid molecules so that they may be purified by coupling to a solid phase support. Sequence-specific probes with different detection tags are hybridized to the resulting mixture of target and competitor nucleic acids, in that the competitor nucleic acid has a slightly different sequence than the target DNA. The amount of signal intensity for both

sequences is compared. Since the initial concentration of the competitor nucleic acid is known, it is possible to extrapolate the concentration of the target nucleic acid from the final competitor nucleic acid concentration.

Combination of References

Applicants respectfully submit that the prior art references do not suggest or provide motivation to make the instant invention. Furthermore, the present invention does not have the same properties as found in the prior art. The present invention relates to a nucleic acid assay useful for detecting, identifying or quantitating a genetic mutation or polymorphism. The advantage of the present invention is that it can detect minute amounts of a test nucleic acid in a large amount of related or similar nucleic acids. Several distinctions exist between the present invention and the references cited by the Examiner. These distinctions are outlined below.

A. The de la Chapelle '808 reference is only useful for detecting the specific polymorphism found at chromosome 2p13-21. No novel methods for determining other DNA mutations are disclosed in de la Chapelle '808.

B. Furthermore, the purpose of the Li '356 invention is to produce an enriched DNA or cDNA library, rather than search for DNA mutations.

C. The Carson '251 method is not useful for detecting small amounts of target DNA in the presence of large amounts of related or similar sequences, as the detection method to determine the target nucleic acid concentration is an ELISA and as such has the same limitations. For example, an ELISA cannot detect a target whose content is as low as 1% of the total specimen. Canson '251 fails to disclose or suggest that small amounts of target DNA can be detected from the presence of large amounts of similar nucleic acids. Also, this method relies on competitive PCR, the reaction conditions of which must be optimized. By contrast, the present invention relies on a competitive hybridization method and can detect target DNA of which content in a specimen is as low as 1%.

Overall, for all of the above reasons, significant patentable distinctions exist between the present invention and cited prior art. Therefore, applicants submit that all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action of the merits of the present application is thereby respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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